Chapter 1

Introduction

1.1 Background

Alzheimer's disease, AD, is a complex and progressive neurodegenerative disease, typically characterized by gradual cognitive decline, short-term memory loss, and impairment of daily functioning (Tryphena et al., 2024). Globally, the prevalence of this disease and related dementia has increased by 160%, from an estimate of 18.7 million in 1991 to 49 million in 2021 (Xiaopeng et al., 2025). In addition, AD has affected a broader age range, amounting to a 211% increase in early-onset AD from 1990 to 2021 (He et al., 2025). This trend reflects the increasing global burden of AD in general.

Throughout the years, studies have been conducted to understand the pathophysiology of this disease. It was discovered that the clinical presentations of AD developed due to the inability of neurons to carry out their functions, as aberrant processing and polymerisation of normally soluble proteins occur, resulting in the buildup of these proteins within the synaptic clefts (Tiwari et al., 2019). In more detail, these deposited proteins are the extracellular amyloid-β plaques and intracellular tangles of hyperphosphorylated tau protein (Zhang et al., 2021). Aside from the most commonly well-known presentations of AD pathogenesis, several studies have discovered that low Mg level is often found in AD patients, indicating that it may be a risk factor for AD and a potential target for adjunctive treatment (Du et al., 2022; Luo et al., 2022; Ben Zaken et al., 2020). Moreover, the reduction of Mg has also been correlated to greater cognitive impairment and higher amyloid burden (Chen et al., 2020).

Mg is one of the most essential macronutrients in the human body, as it is found to interact with more than 300 different enzymes, serving as a cofactor aiding in energy production, protein

synthesis, and DNA and RNA synthesis (Fatima et al., 2024). Within the central nervous system, Mg plays a role in regulating neuronal excitability, synaptic transmission, energy metabolism, and antioxidant defence (Magdaleno & González, 2024). It acts as a natural blocker of the glutamate receptor called N-methyl-D-aspartate (NMDA) receptors, enabling calcium influx regulation and preventing excitotoxic neuronal injury (Wu et al., 2025). It also serves as a cofactor in adenosine triphosphate (ATP)-dependent enzymatic reactions, which is important for supporting adequate energy supply for neuronal signalling and maintenance of membrane potential (Carolina et al., 2023). Additionally, its roles contribute towards stabilization of neuronal membrane, modulating oxidative stress, and also prevent unwanted pro-inflammatory signalling that may otherwise promote neurodegeneration (Patel et al., 2024).

Based on the elaborations, the imbalance of Mg levels can be associated with various neurological disorders, as it may cause reduced synaptic plasticity, increasing vulnerability to oxidative stress, and triggering inflammatory damage (Xue et al., 2019). These effects further strengthen the notion that Mg imbalance may contribute to the progression of neurodegenerative diseases such as AD.

Recent studies have found a correlation between Mg deficiency to AD pathogenesis.

Few studies have investigated whether Mg supplementation modulates AD-associated transcriptional pathways involving amyloid processing, neuroinflammation, tau regulation, and synaptic plasticity simultaneously Hence, to contribute towards the understanding of AD pathogenesis and build a foundation for discovering potential therapeutic targets, this study aims to investigate the neuroprotective role of Mg against AD. This aim will be achieved by observing the effects of Mg supplementation as a preventive and therapeutic intervention in D-galactose and AlCl3 AD-induced mice models towards AD-related genes. The gene of interest will be the genes associated with amyloid processing (BACE1), tau phosphorylation and kinase regulation (GSK3β),

synaptic plasticity and neuronal survival (BDNF), and inflammatory signalling (IL-1β) (Durrant et al., 2020; Chakraborty et al., 2024; Toader et al., 2025; Lopez-Rodriguez et al., 2021).

1.2 Objective

This study aims to investigate the potential neuroprotective role of Mg in AD by assessing the transcriptional changes in key AD-related genes and performing functional enrichment analysis using publicly available datasets to identify molecular pathways and networks modulated by Mg treatment. This aim will be achieved through fulfilling:

- Extract RNA from brain samples obtained from the five groups of mice treated.
- Quantify transcriptional changes of AD-related genes (BACE1, GSK3β, BDNF, IL-1β).
- Validate and complement the experimental findings through bioinformatics analyses of public transcriptomic datasets.

1.3 Hypothesis

Previous findings have reported the correlation between low levels of serum Mg and AD pathogenesis. Moreover, the role of Mg in several molecular pathways, including amyloid processing, tau phosphorylation, neuroinflammation, and synaptic signalling, signifies the potential role of Mg in modulating these processes and providing neuroprotective effects. Based on these observations, the following hypotheses are proposed:

- Primary hypothesis

  Mg supplementation has a significant effect towards the expression of genes involved in amyloid processing, tau phosphorylation, synaptic plasticity, or neuroinflammation in the AD model at the transcription level.

- Specific hypothesis

- AD-induced group will show altered expression of BACE1, BDNF, GSK3β, and/or IL-1β
- Mg supplementation will modulate the expression of one or more AD-related genes compared to untreated AD-induced group.
- Mg treatment may potentially restore partial expression profile of selected genes toward levels observed in healthy controls.

- Null hypothesis

  Mg supplementation shows no significant alterations of BACE1, GSK3β, BDNF, and IL-1β expressions compared to untreated AD controls.